

What is claimed is:

- 1 1. A method for producing double-crosslinked
2 hyaluronate material, comprising the steps of:
 - 3 (a) subjecting hyaluronic acid or a salt thereof to a
4 first crosslinking reaction using either an
5 epoxide compound or a carbodiimide compound as a
6 crosslinking agent, and
 - 7 (b) subjecting the product obtained from step (a) to a
8 second crosslinking reaction using the epoxide
9 compound or carbodiimide compound not used in step
10 (b) as a crosslinking agent, thereby obtaining a
11 double crosslinked hyaluronate material.
- 1 2. The method as claimed in claim 1, wherein the epoxide
2 compound is a polyfunctional epoxide compound.
- 1 3. The method as claimed in claim 2, wherein the epoxide
2 compound is 1,4-butanediol diglycidyl ether (BDDE), ethylene
3 glycol diglycidyl ether (EGDGE), 1,6-hexanediol diglycidyl
4 ether, polyethylene glycol diglycidyl ether, polypropylene
5 glycol diglycidyl ether, polytetramethylene glycol diglycidyl
6 ether, neopentyl glycol diglycidyl ether, polyglycerol
7 polyglycidyl ether, diglycerol polyglycidyl ether, glycerol
8 polyglycidyl ether, tri-methylolpropane polyglycidyl ether,
9 pentaerythritol polyglycidyl ether, sorbitol polyglycidyl
10 ether, or a combination thereof.
- 1 4. The method as claimed in claim 1, wherein the
2 stoichiometry ratio of hyaluronic acid or a salt thereof to
3 the epoxide compound in the crosslinking reaction is about
4 1:50 to 1:1 by crosslinking equivalent.
- 1 5. The method as claimed in claim 1, wherein the epoxide
2 compound is in a solution with a concentration of about 1 to
3 30% by weight.

1 6. The method as claimed in claim 1, wherein the
2 temperature for crosslinking reaction using the epoxide
3 compound as the crosslinking agent is between about 20 and 60
4 °C.

1 7. The method as claimed in claim 1, wherein the time
2 for crosslinking reaction with the epoxide compound as the
3 crosslinking agent is between 10 minutes and 12 hours.

1 8. The method as claimed in claim 1, wherein the
2 carbodiimide compound is 1-methyl-3-(3-dimethylaminopropyl)-
3 carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide,
4 3-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or a
5 combination thereof.

1 9. The method as claimed in claim 1, wherein the
2 stoichiometry ratio of hyaluronic acid or a salt thereof to
3 the carbodiimide compound in the crosslinking reaction is
4 about 1:50 to 1:1 by crosslinking equivalent.

1 10. The method as claimed in claim 1, wherein the
2 carbodiimide compound is in a solution with a concentration
3 of about 0.5 to 30% by weight.

1 11. The method as claimed in claim 1, wherein the
2 temperature for crosslinking reaction using the carbodiimide
3 compound as the crosslinking agent is between about 20 and 60
4 °C.

1 12. The method as claimed in claim 1, wherein the time
2 for crosslinking reaction using the carbodiimide compound as
3 the crosslinking agent is between 30 minutes and 12 hours.

1 13. The method as claimed in claim 1, wherein the
2 hyaluronic acid or a salt thereof is contained in a material.

1 14. The method as claimed in claim 1, wherein, in step
2 (a), the hyaluronic acid or a salt thereof is preformed into
3 a solution, film, membrane, powder, microsphere, fiber,

4 filament, matrix, porous substrate or gel before undergoing
5 the first crosslinking reaction.

1 15. The method as claimed in claim 14, wherein the film
2 is formed by placing a solution of hyaluronic acid or a salt
3 thereof with a concentration of about 1 to 20% by weight in a
4 mold and drying at a temperature between 25 and 70 °C.

1 16. The method as claimed in claim 14, wherein the film
2 has a thickness of about 10 to 500 µm.

1 17. The method as claimed in claim 14, wherein the
2 microsphere is formed by intermittently extruding and
3 dropping a solution of hyaluronic acid or a salt thereof into
4 a coagulant.

1 18. The method as claimed in claim 14, wherein the
2 microsphere has a diameter of about 2.0 to 0.1 mm.

1 19. The method as claimed in claim 14, wherein the fiber
2 is formed by extruding a solution of hyaluronic acid or a
3 salt thereof into a coagulant.

1 20. The method as claimed in claim 1, wherein, in step
2 (b), the product obtained from step (a) is preformed into a
3 solution, film, membrane, powder, microsphere, fiber,
4 filament, matrix, porous substrate or gel before undergoing
5 the second crosslinking reaction.

1 21. The method as claimed in claim 20, wherein the film
2 is formed by placing the product obtained from step (a) in a
3 mold and drying at a temperature between 25 and 70 °C.

1 22. The method as claimed in claim 20, wherein the film
2 has a thickness of about 10 to 500 µm.

1 23. The method as claimed in claim 20, wherein the
2 microsphere is formed by intermittently extruding and
3 dropping the product obtained from step (a) into a coagulant.

1 24. The method as claimed in claim 20, wherein the
2 microsphere has a diameter of about 2.0 to 0.1 mm.

1 25. The method as claimed in claim 20, wherein the fiber
2 is formed by extruding the product obtained from step (a)
3 into a coagulant.

1 26. The method as claimed in claim 1, after step (b),
2 further comprising the following step:

3 (c) washing and drying the double-crosslinked
4 hyaluronate material obtained in step (b).

1 27. The method as claimed in claim 26, wherein step (c)
2 includes washing and drying at a temperature less than 60°C.

1 28. The method as claimed in claim 1, wherein the
2 double-crosslinked hyaluronate material is in the form of
3 solution, film, membrane, powder, microsphere, fiber,
4 filament, matrix, porous substrate or gel.

1 29. A double-crosslinked hyaluronate material produced
2 by the method as claimed in claim 1.